Androgens and the breast

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Abstract

There is increasing interest in the role of androgens in the treatment of women but little is known about their long-term safety. There are also very few studies on testosterone therapy and breast cancer risk. However, some observations support the concept that androgens may counteract the stimulatory effects of estrogen and progestogen in the mammary gland. Mammographic breast density and breast cell proliferation could be regarded as surrogate markers for the risk of breast cancer. Recently the addition of testosterone to a common estrogen/progestogen regimen was found to inhibit the stimulatory effects of hormones on breast cell proliferation. The effects of testosterone alone on the postmenopausal breast remain to be investigated.

Keywords: Androgens; Breast; Cancer

Numerous women all over the world are treated with different combinations of estrogen and progestogen for hormonal contraception and the alleviation of menopausal symptoms. Currently, there is much confusion and an intense discussion about the long-term safety of such hormone therapy. In particular, the effects on the breast have been focused. Clinical and observational studies have reported an increased risk for breast cancer during postmenopausal combined estrogen/progestogen treatment (HT) [1,2].

The fact that sex steroid hormones and their receptors act in concert has stimulated interest in the role of androgens and testosterone in the treatment of women. The androgen receptor (AR) is a third member of the nuclear receptor super family and is a ligand-activated nuclear transcription factor which mediates androgen action [3]. Androgens have been proposed to exert two distinct effects on the mammary gland: (1) In the absence of estrogens and after aromatase conversion they elicit an ER mediated stimulation. This effect can be blocked by treatment with an anti-estrogen; (2) In the presence of estrogens, androgens will act as anti estrogens and inhibit the estrogenic stimulation of growth. This effect is mediated via the AR and can be blocked by anti androgens [4,5].

The most obvious indication for androgen replacement therapy is symptomatic androgen insufficiency caused by pituitary, adrenal or ovarian failure. In many countries, testosterone treatment has gradually become a more accepted component of HT, especially in oophorectomized women. The testosterone therapy can also be considered in young women with premature ovarian failure, e.g., the Turner syndrome, after chemo or radiotherapy or in hypothalamic/pituitary disorders.
Naturally postmenopausal women with symptoms of androgen insufficiency despite conventional HT may also benefit from treatment. Even in premenopausal women with low serum levels of testosterone and symptoms of androgen insufficiency, androgen therapy may be indicated. However, this is still a controversial issue. Little is known about the long-term safety of androgen treatment in women. Some observational data suggest postmenopausal women with high plasma levels of testosterone to have an increased risk of breast cancer, while other studies have found no such association. The interpretation of available data is complex and studies differ by, e.g., methods for testosterone measurement, calculation of free testosterone and adjustment for estrogen status [6].

There are only few studies on exogenous testosterone therapy and breast cancer risk. Dimitrakakis et al. found no increase of breast cancer in a group of postmenopausal women when testosterone was added to HT, during a mean follow-up of 5.8 years [7]. In contrast, recent data from the Nurses Health Study suggest combined estrogen/testosterone to be associated with an increased risk [8]. On the other hand, there are also several observations to support the concept that androgens may counteract the stimulatory effects of estrogen and progestogen in the mammary gland. For example, treatment with flutamide – an androgen receptor antagonist – was shown to markedly enhance breast epithelial proliferation in normally cycling rhesus monkeys. Furthermore, in castrated animals, testosterone addition was found to inhibit breast proliferation as induced by estrogen and progestogen [9]. Women with polycystic ovaries tend to have raised endogenous androgen levels and may also carry a lower breast cancer risk [10]. Androgen receptor dysfunction has been reported in some men with breast cancer [11]. Recently, a genetic linkage was suggested between androgen receptor dysfunction and BRCA-1 mutations [12]. Previously, in fertile women using oral contraceptives, we found an inverse relationship between circulating levels of free testosterone and breast cell proliferation [13]. The need for prospective randomized trials of the effects of testosterone on the normal breast is apparent.

Mammographic breast density and breast cell proliferation could tentatively be regarded as surrogate markers for the risk of breast cancer. Epidemiological studies have repeatedly shown increased breast density to be a strong and independent risk factor. Density reveals the effect of the intrinsic hormonal environment and its background genetics on the breast [14]. In fact, mammographic breast density may represent an intermediate phenotype for breast cancer [15]. We and others have repeatedly demonstrated an increase in mammographic breast density to occur in a significant number of women during conventional HT [16,17]. The basis of risk associated with hormonal therapies may lie in the regulation of cell proliferation. Within populations of cells in vitro and in vivo a higher rate of cell proliferation may increase the risk of transformation to the neoplastic phenotype. In animal models as well as in women, we have shown breast cell proliferation to increase in short term studies on HT [18–20].

Human studies on the effects of testosterone on the breast have been hampered by the lack of preparations suitable for women. However, a transdermal patch releasing 300 µg of testosterone per day is currently being evaluated in clinical trials in postmenopausal women [21]. Using this patch, we recently carried out a six months prospective randomized double-blind placebo controlled study [22]. Postmenopausal women were given continuous combined estradiol 2 mg/norethisterone acetate 1 mg and were equally randomized to receive additional treatment with either the testosterone patch or a placebo patch. Breast cells were collected by fine needle aspiration biopsies at baseline and after six months. In the placebo group and in agreement with previous reports there was a more than five-fold increase in total breast cell proliferation from baseline to six months. In contrast, during testosterone addition no significant increase in breast cell proliferation was recorded. The different effects of the two treatments were apparent in both epithelial and stromal breast cells. These results indicate that the addition of testosterone to a common estrogen/progestogen regimen may have a potential to modulate the stimulatory effects of hormones on breast cell proliferation. The effects of testosterone alone on the postmenopausal breast in women not receiving simultaneous estrogen/progestogen treatment remain to be investigated.

References